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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/830,839	02/19/2002	Ajit Lalvani	7096-102XX / 10103632	3551

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EXAMINER	
MINNIFIELD, NITA M	

ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 07/27/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/830,839	LALVANI ET AL.	
	Examiner	Art Unit	
	N. M. Minnifield	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 May 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *See Continuation Sheet* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *27-31,33,34,36-46,48,49,51-55,57,58,60-62,64,65,75,76,78,79,81 and 82* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892) 2 sheets

2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.

4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.

5) ☐ Notice of Informal Patent Application (PTO-152)

6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims pending in the application are 27-31,33,34,36-46,48,49,51-55,57,58,60-62,64,65,75,76,78,79,81 and 82.

DETAILED ACTION

Response to Amendment

1. Applicants' amendment filed May 12, 2004 is acknowledged and has been entered. Claims 28, 36, 53-55 and 60-62 have been amended. Claims 27-31, 33, 34, 36-46, 48, 49, 51-55, 57, 58, 60-62, 64, 65, 75, 76, 78, 79, 81 and 82 are now pending in the present application. All rejections have been withdrawn in view of Applicants' amendment and/or comments with the exception of those discussed below.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

3. Claims 27-31, 33, 34, 36-46, 48, 49, 51-55, 57, 58, 60-62, 64, 65, 75, 76, 78, 79, 81 and 82 are rejected under 35 U.S.C. 102(e) as being anticipated by Andersen et al (5955077).

The claims are directed to methods of determining infection in an human patient by, or exposure of a human patient to mycobacterium which expresses ESAT-6 comprising the method of contacting a population of T cells from the patient with the peptide represented by SEQ ID NO: 1 (ES1) and optionally other peptides from SEQ ID NO: 2-11, and to kits for carrying out the method. The peptides can also be a peptide wherein the peptide is substituted by an analogue; the peptide analogue has one or more deletions or conservative substitutions.

Andersen et al discloses the polypeptide ESAT-6 as well as the amino acid sequence (SEQ ID NO: 2). The peptides (SEQ ID NO: 1-11) claimed by

Applicants are set forth in disclosed SEQ ID NO: 2. The prior art discloses methods for diagnosing tuberculosis (abstract; col. 11). Andersen et al discloses that analogues and subsequences of the polypeptides can be used so long as it has the same immunological characteristics as the polypeptide (col. 2, l. 50-55). The analogue and subsequence of the polypeptide are of a "...similar amino acid sequence as shown in SEQ ID NO: 2, allowing for minor variations which do not have adverse effect on the ligand binding properties and/or biological function and/or immunogenicity, or which may give interesting and useful novel binding properties or biological functions and immunogenicities etc." (col. 2, l. 60-67). "Furthermore, in the present context the term "immunologically equivalent" means that the analogue or subsequence of the polypeptide is functionally equivalent to the polypeptide with respect to the ability of evoking a protective immune response against tuberculosis and/or eliciting a diagnostically significant immune response (e.g. a DTH reaction)." (col. 3, l. 4-10; see also col. 3, l. 41-47). Andersen et al discloses that in immunodiagnostics it is often possible and practical to prepare antigens from segments of a known immunogenic protein or polypeptide, that certain epitopic regions may be used to produce responses similar to those produced by the entire antigenic polypeptide, and that these potential antigenic or immunogenic regions can be identified by known methods (col. 11, l. 9-25). Andersen et al discloses a peptide, which comprises an epitope for a T-helper cell (col. 11, l. 27-28). Andersen et al discloses methods of diagnosing tuberculosis caused by *M. tuberculosis*, *M. bovis* or *M. africanum* in an animal, including a human being, comprising intradermally injecting, in the animal, a pharmaceutical composition containing a polypeptide as defined or an analogue and/or subsequence thereof which is immunologically equivalent to the peptide, a positive

skin response at the location of injection being indicative of the animal having tuberculosis, and a negative skin response at the location of injection being indicative of the animal not having tuberculosis (col. 14, l. 6-17). Andersen et al discloses that when "diagnosis of previous or ongoing infection with virulent mycobacteria is the aim, a blood sample comprising mononuclear cells (i.e. T-lymphocytes) from a patient could be contacted with a sample of one or more polypeptides of the invention. This contacting can be performed in vitro and a positive reaction could e.g. be proliferation of the T-cells or release cytokines such as -interferon into the extracellular phase (e.g. into a culture supernatant). Finally, it is also conceivable to contact a serum sample from a subject to a contact with a polypeptide of the invention, the demonstration of a binding between antibodies in the serum sample and the polypeptide being indicative of previous or ongoing infection." (col. 14, l. 35-47; see also col. 14, l. 48-62; figures; Example 5, cols. 29-30). Andersen et al discloses the use of ESAT6 as a diagnostic agent on a skin test (see Example 6, col. 31, l. 5-17). Andersen et al discloses that the mycobacterium can be *M. tuberculosis*, *M. bovis* or *M. africanum* (col. 2, l. 27-31). Andersen et al discloses diagnostic kits for the diagnosis of on-going or previous TB infections comprising peptides and means for detecting the interaction with the relevant substance reacting with peptide (col. 12, l. 30-43).

The prior art of Andersen et al discloses the claimed methods and kits.

The rejection of claims 27-31, 33, 34, 36-46, 48, 49, 51-55, 57, 58, 60-62, 64, 65, 75, 76, 78, 79, 81 and 82 under 35 U.S.C. § 102(e) as anticipated by Andersen et al (5955077) is maintained. This rejection is maintained for

essentially the same reasons as the rejection of claims 27-31, 33, 34, 36-46, 48, 49, 51-55, 57, 58, 60-62, 64, 65, 75, 76, 78, 79, 81 and 82 under this statutory provision, as set forth in the last Office action. Applicants' arguments filed May 12, 2004, have been fully considered but they are not deemed to be persuasive.

Applicants have asserted that Anderson et al patent, which is based on PCT/DK94/00273 (published as WO 05/01441) cannot rightly be seen as disclosing the invention now claimed, or rendering it obvious, since it does not direct the selection of the peptide ESI (the N-terminal 15 amino acid fragment of the *M. tuberculosis* protein ESAT-6) for diagnostic use in humans. This is the peptide represented by SEQ. ID. NO: 1 in the subject application and the essential peptide specified in claim 1.

However, it is noted that the Examiner interprets the claim language broadly. The recitation of "the peptide represented by SEQ ID NO: 1", does not exclude additional amino acids outside of those specifically set forth in SEQ ID NO: 1. The Examiner views this as comprising or open claim language. The prior art discloses the claimed invention.

Applicants have asserted that the Andersen et al. US Patent teaches purification of ESAT-6 from a crude culture filtrate and includes reference to diagnostic use but includes no more than very general speculation about diagnostic use of ESAT-6 fragments. Disclosure of the amino acid sequence of ESAT-6 *per se* is not a disclosure of any particular fragment or fragments for any diagnostic use. Moreover, the only relevant example, Example 6 merely reports skin testing of purified whole ESAT-6 in guinea pigs. The specification provides no teaching whatsoever of assistance in selecting T cell epitope-containing peptides for

diagnostic use in humans. It certainly does not direct selection of the N-terminal peptide ES1.

However, as previously noted Anderson et al discloses that in immunodiagnostics it is often possible and practical to prepare antigens from segments of a known immunogenic protein or polypeptide, that certain epitopic regions may be used to produce responses similar to those produced by the entire antigenic polypeptide, and that these potential antigenic or immunogenic regions can be identified by known methods (col. 11, l. 9-25). Andersen et al discloses a peptide, which comprises an epitope for a T-helper cell (col. 11, l. 27-28). Andersen et al discloses methods of diagnosing tuberculosis caused by *M. tuberculosis*, *M. bovis* or *M. africanum* in an animal, including a human being, comprising intradermally injecting, in the animal, a pharmaceutical composition containing a polypeptide as defined or an analogue and/or subsequence thereof which is immunologically equivalent to the peptide, a positive skin response at the location of injection being indicative of the animal having tuberculosis, and a negative skin response at the location of injection being indicative of the animal not having tuberculosis (col. 14, l. 6-17). Andersen et al discloses that when "diagnosis of previous or ongoing infection with virulent mycobacteria is the aim, a blood sample comprising mononuclear cells (i.e. T-lymphocytes) from a patient could be contacted with a sample of one or more polypeptides of the invention. This contacting can be performed in vitro and a positive reaction could e.g. be proliferation of the T-cells or release cytokines such as -interferon into the extracellular phase (e.g. into a culture supernatant). Finally, it is also conceivable to contact a serum sample from a subject to a contact with a polypeptide of the invention, the demonstration of a binding between antibodies in the serum sample

and the polypeptide being indicative of previous or ongoing infection." (col. 14, l. 35-47; see also col. 14, l. 48-62; figures; Example 5, cols. 29-30). Andersen et al discloses the use of ESAT6 as a diagnostic agent on a skin test (see Example 6, col. 31, l. 5-17).

Further, a US Patent is presumed valid and enabled. Since every patent is presumed valid (35 U.S.C. 282), and since that presumption includes the presumption of operability (Metropolitan Eng. Co. v. Coe, 78 F.2d 199, 25 USPQ 216 (D.C. Cir. 1935), examiners should not express any opinion on the operability of a patent. Affidavits or declarations attacking the operability of a patent cited as a reference must rebut the presumption of operability by a preponderance of the evidence. In re Sasse, 629 F.2d 675, 207 USPQ 107 (CCPA 1980).

Further, since in a patent it is presumed that a process if used by one skilled in the art will produce the product or result described therein, such presumption is not overcome by a mere showing that it is possible to operate within the disclosure without obtaining the alleged product. In re Weber, 405 F.2d 1403, 160 USPQ 549 (CCPA 1969). It is to be presumed also that skilled workers would as a matter of course, if they do not immediately obtain desired results, make certain experiments and adaptations, within the skill of the competent worker. The failures of experimenters who have no interest in succeeding should not be accorded great weight. In re Michalek, 162 F.2d 229, 74 USPQ 107 (CCPA 1947); In re Reid, 179 F.2d 998, 84 USPQ 478 (CCPA 1950).

It is also noted that the claims do not set forth that the claimed method is an improvement over the known methods of tuberculosis diagnosis.

Applicants have referred to other publications, however, it is noted that the Examiner has not set forth these references as part of the prior art rejection.

4. Claims 53-55, 57 and 58 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: is this an in vitro or in vivo assay or something else? Part (i) of claim 53 recites "administering..."; administering to what or to whom?

5. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

6. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however,

will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to N. M. Minnifield whose telephone number is 571-272-0860. The examiner can normally be reached on M-F (8:00-5:30) Second Friday Off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette R.F. Smith can be reached on 571-272-0864. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

N. M. Minnifield
Primary Examiner
Art Unit 1645

NMM
July 20, 2004